



MODULE 5: ACCEPTABILITY

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1. INTRODUCTION

In all disease areas, despite the availability of effective molecules, formulations adapted for children are still lacking and their development falls behind that of formulations for adults. Children are often either not treated or, based on anecdotal paediatric evidence, treated off label or off licence with formulations for adults (1–5).

During the past two decades, new legislation and regulation-related guidance from the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are progressively changing this situation with the mandated concurrent development of formulations for adults and for children (6–11).

Other countries have introduced policies to enhance the labelling of products for children (12): in Japan, by extending a product's re-examination period; in Canada, through a six-month extension of data protection providing acceptability and efficacy data for children; and, in Switzerland, through the obligation to submit paediatric plans and incentives for including data in the medicine label in accordance with the agreed plans. India and China are becoming important pharmaceutical industry actors, and their legislation is being revised to include specific provisions for developing drugs for children.

Pharmaceutical companies are now required to consider very early in a new drug's development the specific needs of children (13) in terms of therapeutic indication and the appropriateness of the envisioned drug formulations for the relevant target populations.

In parallel with regulations mandating the development of formulations for children for new or innovative medicines, the EMA paediatric-use marketing authorization is a dedicated marketing authorization covering indications and appropriate formulations for medicines that are developed exclusively for children, for products

already authorized that are no longer covered by patents. This includes over-the-counter products for which safety and acceptability may be problematic. With the incentive of additional data and marketing protection, the paediatric-use marketing authorization aims at transforming off-label use of drugs into safer and better circumscribed authorized use. Similarly, the Best Pharmaceuticals for Children Act in the United States provides incentives to encourage the performance of studies involving children that provide data on the effectiveness, safety and appropriateness of medicines already on the market for same or expanded indications.

Although determining the formulation type, dose and intake frequency that provide adequate drug exposure across all age or weight bands is an essential component of developing drugs for children, the acceptability of the formulation itself also needs to be maximized, since it partly conditions adherence and ultimately treatment effectiveness and safety (14).

The objective of this module is to discuss issues around formulation acceptability and to assist scientists and organizations confronted with the development of age-appropriate medicines for children. The module focuses on product development strategies for oral dosage forms – solid and liquid – although other forms, such as long-acting injectables or inhalants, may play an increasing role in therapy for children. Importantly, although the theme of this initiative is developing better antiretroviral (ARV) formulations for children living with HIV, the scope of the discussion extends to other therapeutic fields, such as antibiotics and antituberculosis drugs, medicines for diseases of the blood and blood-forming organs and cancer and malaria therapy, where acceptability may be key, as well as medications for chronic conditions.

2. BACKGROUND

The EMA defines acceptability as “the overall ability and willingness of the patient to use and its caregiver to administer the medicine as intended” (11). The word “medicine” refers here to the therapeutic entity as it is to be delivered to the end user. This includes the type of dosage form, its formulation: composition and appearance (tablet size, shape and colour), the dose of its specific active substance, dosing frequency, packaging, medical device, dosing devices, container closure system together with written user’s instructions (product label and package leaflet) (15)

Acceptability, in this context, is essentially a characteristic of the product and of how it is delivered. Acceptability may significantly affect adherence – behaviour rather than a characteristic of the patient or caregiver – and may secondarily affect efficacy and safety. However, the precise contribution of acceptability to adherence is difficult to establish (16,17). However, from an ethical viewpoint that considers the inherent vulnerability of children and adolescents, acceptability needs to be maximized regardless of how it affects clinical outcomes.

Clinical appropriateness is a somewhat broader concept than acceptability, referring to the medicine characteristics that determine whether, in their personal environment and life situation, children and/or their caregivers can use the medicine as intended. For example, the need for refrigeration is a major economic and practical obstacle to the use of some liquid formulations in tropical climates. Appropriateness for children is discussed in detail in several reflection papers by WHO, the EMA and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (10,18–20). The FDA and the EMA (11,18) have also issued various recommendations on designing age-appropriate medicines for children (21).

In commentary on the EMA guidelines (11), Piotr Kosarevitz (22) states:

As a general rule, acceptability aspects should be embedded in the development programme and evaluated, (preferably) during the clinical study (preferably) with patients from all target age group(s). ...The choice of the acceptability testing method and acceptance criteria (to determine whether the medicine dosage form is considered acceptable or not), should be described and justified, taking into account the characteristics of the target age group, the condition relevant to the medicine, incidental and multiple use, co-medication and differences between countries

In compliance with regulators’ requirements, pharmaceutical companies must submit their initial paediatric investigation plans (for the EMA) or paediatric study plans (for the FDA) early in the drug development process. Paediatric investigation plans are submitted slightly earlier than paediatric study plans, and both need to be agreed on with regulators before approval of products for adults. Plans describe and justify the age appropriateness of the formulations envisioned for the relevant children (and justify waivers for specific groups of children).

Although they may be modified during drug development, paediatric investigation plans (and paediatric study plans) should provide sufficient data to enable the assessment of the medicinal product quality (including acceptability), safety and efficacy in children and thus its benefit–risk profile for children (23).

Moreover, if formulations already exist for the subsets of the children in question, their suitability should be discussed.

In its published scientific document template for a paediatric investigation plan application, the EMA specifies further its expectations for formulations adapted for children.

The section of the paediatric investigation plans and paediatric study plans on developing formulations for children should address critical issues, such as:

- the need for a specific formulation, pharmaceutical form, strength or route of administration in relation to the chosen subsets or age groups of children and the benefit of the chosen formulation, pharmaceutical form, strength or route of administration;
- potential issues related to excipients and children's (anticipated) exposure levels;
- the administration of the medicine to subsets of children, including acceptability, use of specific administration devices, ability to mix with food and possible use with a nasogastric tube; and
- the precision of dose delivery and/or dose accuracy for any pharmaceutical form for the anticipated dose for children and indicated age range.

If, based on scientific justifications, a formulation or pharmaceutical form relevant and acceptable for children cannot be developed on an industrial scale, the applicant should state how it intends to facilitate the industry-verified or extemporaneous preparation of an individual ready-for-use formulation for children.

Despite little empirical evidence, it is generally accepted that the availability of better age-adapted formulations would reduce the risk of medication and dosing errors and increase the overall safety and effectiveness of treatment (14). Although they may still play an important role in the drug development approaches, traditional liquid formulations present important limitations in terms of stability, palatability and costs. For children, the development of liquids has shifted to solid formulations in the past two decades (24,25). Children and caregivers prefer solid oral dosage forms, including tablets, capsules, mini-tablets or pellets and chewable, dispersible and multi-particulate dosage forms

(15), which tend to replace liquid dosage forms: syrups, solutions, emulsions and suspensions (Table 5.1) (26).

To achieve the targeted drug exposure, more than one dosage form and/or strength may be needed to cover the range of ages and weight bands as children grow and mature. Alternative administration strategies with flexible formulations may be considered for children who cannot be accommodated by a specific dosage form: such as segmenting or crushing tablets, co-administration with food or liquids or multi-use formulations such as dispersible chewable tablets (11).

Although children and caregivers have an opinion about what are the most desirable types of formulations, preference does not equal acceptability (27). For older children and adolescents, for example, lifestyle and peer pressure greatly influence medication preferences.

Table 5.1. Advantages and disadvantages of various oral formulations for children

Oral dosage forms	Dose flexibility	Dose preparation	Ease of ingestion	Tolerability and safety
Syrup, solution, drops	High (with limits for drops)	Need for measuring device	Easy to swallow; palatability and volume are possible issues	May require buffers, co-solvents, flavours, sweeteners; multidose containers may need preservatives
Emulsion	High	Requires measuring device and shaking for homogeneity	Easy to swallow; palatability and volume are possible issues	May require flavours, sweeteners; multidose containers require preservatives and surfactants
Suspension	High	Requires measuring device and shaking for homogeneity	Easy to swallow, uncertain palatability, consider volume, gritty sensation possible	Multidose containers require preservatives and may require buffers, surfactants, flavours or sweeteners
Effervescent or dispersible tablet	Low	Suitable volume and quality of water for dissolution and dispersion	Easy to swallow; palatability and volume are possible issues	May require flavours, sweeteners; consider sodium, potassium and bicarbonate content
Multi-particulates, granules, powders	Medium to high	Appropriate use of measuring device or packaging; may need food or liquid vehicle	Easy to swallow; from birth on if dispersed in liquid, from six months on with semi-solid food; dose, volume, texture and palatability require consideration	Risk of aspiration or choking when not dispersed
Tablets	Low	No preparation	Difficult to swallow for younger children, depending on size and shape; limited organoleptic issues	Risk of aspiration or choking; ability to swallow limited for younger children; lack of data on age versus suitable size
Hard gelatin capsules	Low	May need preparation if administered with food or liquid	Difficult to swallow for younger children, depending on size; limited organoleptic issues	Risk of aspiration or choking; risk of gelatin shell sticking to gastrointestinal mucosa; gelatin may not be acceptable in some cultures – alternatives exist
Soft gelatin capsules	Low	No preparation	Difficult to swallow for younger children, depending on size; limited organoleptic issues	Like hard gelatin capsules; potential risk of chewing
Mini-tablets (1–4 mm)	Medium	Multiple mini-tabs may require counting; device or packaging – manual dexterity	Easier to swallow than conventional tablets; limited organoleptic issues	Risk of aspiration or choking, especially for children younger than two years if coated
Oro-dispersible tablet or melt	Low	No preparation; water not necessary	Easier to swallow than conventional tablets; taste and grittiness are the main considerations	Risk of aspiration or choking; may require flavouring or sweeteners
Chewable dosage forms	Low	No preparation	Should be chewed and not swallowed; palatability may be an issue	Risk of aspiration or choking; may require flavouring or sweeteners; risk of intestinal obstruction if swallowed whole
Oral films (dispersible)	Low	No preparation, water not necessary – manual dexterity	Easy to swallow	May require plasticizers, flavours or sweeteners

Source: reprinted from Int J Pharm., 536, Walsh J, Ranmal SR, Ernest TB, Liu F, Patient acceptability, safety and access: a balancing act for selecting

	Risk of incorrect dosing	Stability – shelf life in use	Development and manufacturing complexity	Supply chain	Relative cost
	Incorrect use of measuring device	Less stable than solids; microbiological contamination in use; compatibility with primary packaging	Simple development, routine manufacturing and packaging	Bulky and heavy for transport and storage; may need refrigeration	Low
	Incorrect use of measuring device; shaking for homogeneity and dose uniformity	Less stable than solids; microbiological contamination; thermodynamic instability	Development can be complex; routine manufacturing and packaging	Bulky and heavy for transport and storage; may need refrigeration	Medium to high
	Incorrect use of measuring device; shaking for homogeneity and dose uniformity	Less stable than solids; microbiological contamination; physical instability	Development can be complex; routine manufacturing and packaging	Bulky and heavy for transport and storage; may need refrigeration	Medium
	Need to absorb full dispersion volume and residue	Moisture sensitivity; solution or dispersion of limited stability	Simple development; routine manufacturing and packaging; low-humidity conditions and modified tooling	Easier transport and storage	Low to medium
	Risk of incorrect dosing for products requiring dose measurement; incomplete dosing if the food or beverage vehicle is incompletely consumed; reconstitution errors for powder for suspensions	Good stability; compatibility with food or beverage vehicle to be verified	Complexity depends on technology; routine packaging with standard equipment; can serve as intermediate for other dosage forms	Easier transport and storage	Low to medium
	Low risk of incorrect dosing, except if tablet manipulated	Good stability	Not complex; routine packaging with standard equipment	Easier transport and storage	Low
	Low risk of incorrect dosing and incorrect use	Good stability	Non-complex development process; routine manufacturing and packaging process	Easier transport and storage	Low
	Low risk of incorrect dosing and incorrect use	Potentially less stable than tablets; may be sensitive to high temperature and humidity	Requires specialist development and manufacturing processes; routine packaging with standard equipment	Easier transport and storage; may be sensitive to high temperatures and humidity	High
	Risk of incorrect dosing if multiple mini-tablets required per dose	Good stability	Non-complex development process; routine manufacturing and packaging process; content uniformity a challenge	Easier transport and storage	Low
	Low risk of incorrect dosing and incorrect use	Good stability; may require moisture protective packaging	Complexity depends on technology; routine packaging with standard equipment; or specialist process and equipment (lyophilizates)	Easier transport and storage	Low to high
	Low risk of incorrect dosing and incorrect use	Good stability; may require moisture protective packaging	Complexity depends on technology; routine packaging with standard equipment; or specialist process and equipment (deposited formulations and softgels)	Easier transport and storage	Low to medium
	Low risk of incorrect dosing	Good stability; requires moisture-protective packaging	Requires specialist development, manufacturing and packaging processes	Easier transport and storage	Medium to high

3. CHALLENGES

There are multiple challenges in developing better acceptable formulations for children. Most obvious is the lack of consensus around what acceptability means and consequently the lack of guidance from regulators on how it should be evaluated. Another difficulty arises from the fact that acceptability is only one attribute of formulations appropriate for children. Other considerations include stability, absorption, disease, safety and cost. Formulations for children are often considered late in development, when efficacy and safety for adults begins to be known and when stability and pharmacokinetic data have already started to be accumulated. Another difficulty is that acceptability is not an inherent property of the product; it is also defined by the end-users: the children and their caregivers. Finally, standardized methods and quality assurance are lacking for assessing the acceptability of formulations ranging from solid oral dosage forms such as tablets, capsules, mini-tablets and pellets, to chewable, dispersible, multi-particulate dosage forms and liquid dosage forms such as syrups, solutions, emulsions and suspensions. The following sections describe these difficulties in greater depth and explore what solutions can be found.

3.1 Lack of guidance from regulators and varying definitions of acceptability

European and United States regulators require that pharmaceutical companies describe and justify in their development plans the choice of their formulations for all target populations and require that they document and report the acceptability of their formulations, but they offer little guidance on what studies should be performed and reported to comply with this requirement.

How acceptability is understood and defined obviously depends on the question asked. Here the essential question is to determine whether a formulation proposed for registration is acceptable for the relevant target populations of children: can the claim for age-appropriate medicines for children be effectively substantiated? However, published studies show extreme variation in how acceptability is defined and assessed.

In the most recent reviews examining various aspects of acceptability of pharmaceutical dosage forms, the multiplicity of keywords used to identify relevant literature confirms this variation and confusion around the concept of acceptability. Published literature searches most often include such words as acceptance, adherence, tolerability, satisfaction, preference, palatability, taste and swallowability (28).

Because paediatric investigation plans and paediatric study plans must be submitted at the very beginning of clinical development of the medication (for adults: Phase I in Europe and Phase II in the United States), at the time of these first trials, the real constraints of the formulations for children are not yet known. Pharmaceutical companies may therefore not want to or be able to describe the envisioned dosage form for children in a detailed manner.

Following the submission of the paediatric investigation plans and paediatric study plans, regulators may request clarification about the target group or the choice of formulation. Although interactions between regulatory agencies and pharmaceutical companies are not public, a review by the EMA of the paediatric investigation plans submitted to the Paediatric Committee during the first years of implementation of the paediatric regulations indicated that in 82% of the cases, the excipients were questioned (their justification, dosage

and the possibility of avoiding them through alternative formulations); in half the cases, testing for palatability and acceptability was discussed; and in 23% of cases, formulations and practical issues related to manipulations or small volumes were considered problematic (13).

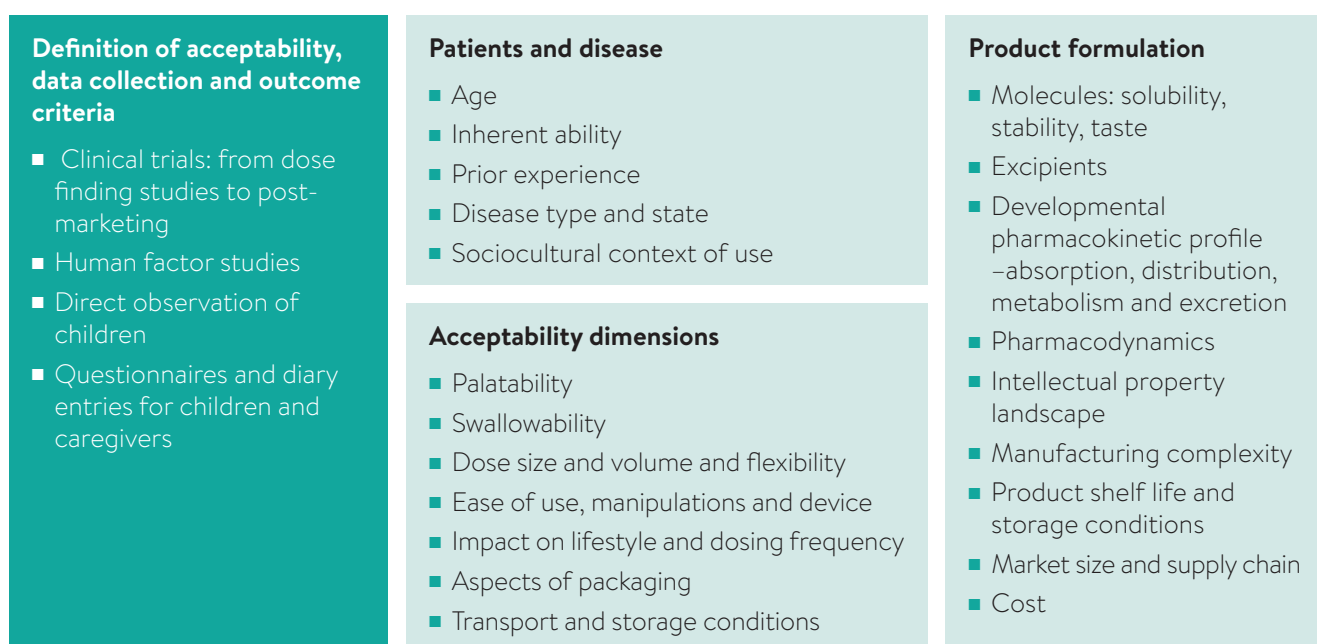
In another review covering 2007– 2011 (29), 150 paediatric investigation plans were examined (16 therapeutic areas and 220 oral dosage forms in 431 strengths and compositions). One third of the paediatric investigation plans involved tablets, 20% liquids and 16% dosage forms stored as a solid but swallowed as a liquid, such as dispersible tablets. According to this report, the Paediatric Committee review and interactions with pharmaceutical companies resulted in an increase in the number of oral dosage forms or a modification of their specific composition or strength. For many paediatric investigation plans, the target age range was widened and the excipient composition and usability aspects modified (30,31).

3.2 Dosage forms for children are a necessary compromise between stability, absorption, disease, safety, cost and acceptability

The ideal formulation should have flexible dosage increments and minimal excipients, be palatable, safe and easy to administer and be stable with regard to light, humidity and heat (Fig. 5.1) (32). However, as stated by Walsh et al. (26), “a single ideal dosage form does not exist”.

The development of age-appropriate medicines for children is constrained (33) by the characteristics of the target population of children (age group) and by the characteristics of the molecules (solubility, stability and taste), their age- and development-dependent pharmacokinetic profiles (absorption, distribution, metabolism and excretion), their pharmacodynamic profiles (therapeutic window, mode of action and toxicity), the disease and the disease stage

Fig. 5.1. Medicine formulations: a compromise between stability, absorption, disease characteristics, safety and cost



(forgiveness and acute versus chronic condition), the circumstances of use (clinic, home, nursery, school or other), the intellectual property landscape, the manufacturing and packaging complexity, the product shelf life and storage conditions, the market size and the supply chain and cost, which ultimately determines access.

The characteristics of the final product therefore represent a compromise between multiple constraints (Fig. 5.1). When suboptimal formulations are finally obtained, mitigation strategies can be developed to minimize the impact on acceptability. Risk-based strategic approaches to innovation could guide the selection of formulations (27,34), but within this process, acceptability has often been considered an adjustment variable resulting in pharmaceutical products that remain poorly adapted to children.

3.3 The influence of the user and the medicinal product cannot be studied separately

The characteristics of the user and those of the medicinal product drive acceptability (35,36). Although distinguishing what relates to the user and what relates to the dosage form is useful, they cannot be disentangled since acceptability is precisely what links formulation characteristics with specific target groups.

3.4 Acceptability studies are often carried out late

Although the development of formulations for children can still continue after products for adults have been registered along a timeline based on agreed commitment to the EMA and FDA, and acceptability questions can be addressed during the whole duration of development, in practice the window of opportunity during which acceptability can be assessed and the formulation modified is short (37). As explained above, the characteristics of the product only begin to be known when

the paediatric investigation plan or paediatric study plan is submitted, and it is only when the first formulation prototype is available that acceptability can be truly evaluated in the target population and the formulation possibly modified. The prototype formulation can be intermediate of the intended final formulation for children or derived from the existing formulation for adults. Using such a prototype often requires performing a bioavailability study to ensure that it leads to the same active ingredient exposure as the final commercial formulation (unless a biowaiver is granted based on the solubility and permeability properties of the active ingredient). Produced under good manufacturing practice standards that ensure reproducible bioavailability, it can later be bridged to the final commercial preparation (38,39).

3.5 Standardized methods and quality assurance for assessing acceptability are lacking

After almost 10 years of implementation of the paediatric regulations, both in the United States and in Europe, many experts have investigated how the acceptability of formulations for children is assessed and reported. All reviews stressed the lack of standardized methods for assessment and of quality assurance (13,14,28,36,40–45).

In the studies that are published, the domains of acceptability explored vary considerably, with palatability being, by far, the most common attribute measured. Little to no information is provided about how data capture tools are developed and validated or the precautions taken to avoid interviewer bias. Hypotheses tested and criteria for acceptability are rarely clearly stated.

Research reports hardly ever define what is considered “acceptable”. Although the acceptability threshold used in veterinary research (44) is relatively unambiguous, no such criteria are available for humans. Percentages or scores based on ad hoc summarized or regrouped direct or proxy measurements of

acceptability reported in published studies cannot be readily interpreted.

However, most of the acceptability studies for product registration have not been published. In a review of the studies involving children listed in the clinicaltrials.gov database in preparation for a symposium, Pinto & Selen (46) note that the results of palatability and swallowability studies are simply not communicated. Of 7259 studies listed, 874 provide study results, but none on swallowability and only two on palatability (46).

Published articles report few aspects of acceptability, with limited evaluation of acceptability dimensions, limited categories of information providers and large variation in assessment approaches and tools (42).

As explained above, as a result of the incentives and mandatory requirements from stringent regulatory agencies, the development of drugs for children is systematically initiated in parallel to the development of drugs for adults, and more formulations for children will become available, although their acceptability does not or perhaps cannot take precedence over other key attributes such as efficacy, pharmacokinetics or stability.

ARV medicines clearly exemplify this situation. The first anti-HIV molecules marketed in the early 1990s had severe toxicity and limited efficacy and formulations for children comprised at best liquid forms that were difficult to procure, store and administer. In many low- and middle-income countries where the HIV epidemic was most severe, the only way to keep children with HIV alive was to treat them with a mix of syrups and solutions and fractions of adult tablets.

The first palatable, easy-to-take fixed-dose combination became available in 2007. Triomune Baby® (6 mg stavudine + 30 mg lamivudine + 50 mg nevirapine) and Triomune Junior® (double these concentrations) were the first fixed-dose combinations licensed for children younger than 12 years. They were scored so that they could easily be broken in half, allowing use within a simple weight-band dosing table.

However, the more potent option for newborn infants, lopinavir/ritonavir solution, was a heat-unstable, foul-tasting solution with 45% alcohol and 17% propylene glycol. It was only in 2015 that a better adapted multi-particulate lopinavir/ritonavir solid-pellet formulation received regulatory approval. Nevertheless, this formulation cannot be given safely to newborns, is difficult to administer by caregivers and is poorly accepted by children because of its remaining bitter taste.

In a report of the M-CERSI paediatric formulation development workshop in 2016 through the University of Maryland's Center of Excellence in Regulatory Science and Innovation, Robert Ternik and colleagues have compiled the various approaches used to assess and document palatability and swallowability (34).

Palatability

Many approaches have been used to assess palatability in children (47–49).

With the rank order or preferential method, the subject is asked to place products in order of preference or choose the one they prefer. Evaluation is brief and does not involve sustained attention and is therefore suitable for young children.

With the facial action coding system, children are exposed to stimuli and the facial expressions are videotaped; however, this approach is time consuming and costly (50).

With scaling methods, subjects older than five years are presented samples and asked to select the likeness of sensation on a scale (51,52).

Scaling methods include:

- facial hedonic scales: these are a scale from 2 to 10 with pictorial descriptors (43) that can be used with children as young as three years old, but cognitive maturity may influence the results (52,53);
- visual analogue scale: a scale from 10 to 100 points on a horizontal 10-cm line, anchored with word descriptors at each end (43,52)

- Likert scale: it assigns 5–11 points to verbal descriptors, ranging from “extremely weak” to “extremely strong”; and
- labelled magnitude scale (54), a hybrid scale with verbal descriptors on a quasi-logarithmic vertical scale, suitable for describing the taste intensity of highly divergent samples because of its broad scaling (54)

Finally, with verbal response (descriptive methods), children are asked to rate preference using verbal descriptors such as “no taste” to “very strong taste”. This method is more discriminating than scaling methods (34) but is not suitable for younger children who cannot visualize and accurately use the descriptors.

Swallowability

Palatability is subjective, but swallowability is more objective since it describes an ability of children rather than an appreciation. Most studies used direct observation, investigating children’s mouths after administration. Few studies used questionnaires or diary entries to provide parents’ reports of the outcomes of swallowing or whether or not a problem in swallowing the product occurred (28,29,55,56). The difficulty lies in defining the outcome: “everything swallowed”, “smooth swallowing”, “swallowing with a choking reflex or cough” and “biting or chewing followed by swallowing” (34). For palatability, children’s cooperation highly influences the assessment.

Ease of use

Ease of use is a third major component of the acceptability of a medicine. Human factor studies are designed to evaluate the user interface of a product (57). Drug development should consider the user interface and factors that can reduce the risk of medication errors. Since children are often dependent on a caregiver for preparing and taking the drug, such studies may not involve young children. Human factor studies are typically conducted with representative users to evaluate the ability of the user to perform critical tasks to

understand the information in the packaging and labelling. Formative studies may be conducted during the iterative product development process to assess user interaction with the product and identify potential difficulties or errors in use. They are followed by human factor (simulated or actual-use) validation studies to demonstrate that the intended users can use the final product without serious errors or problems under the expected use conditions. In situations when understanding the information provided in the labelling of a combination product is critical to using a product safely and effectively, a study to assess the user’s understanding of such information is appropriate. Knowledge task studies may be carried out as part of the formative or validation process. Use-related risk analysis helps to identify the critical tasks to be evaluated in a human factor study, inform the priority for testing the tasks and determine whether specific use scenarios should be included in testing. The analysis should consider all the intended uses, users and use environments; therapeutic or diagnostic procedures associated with the use of the product; similar products used within the environments; and any associated medical factors that may affect the safe and appropriate use of the product.

There is considerable need for developing an operational and pragmatic definition of swallowability and palatability and for establishing a simple, standardized method for evaluating all dimensions of acceptability, swallowability, palatability and ease of use. Researchers in the field stress the need to bridge in vitro and in vivo data and to develop new technologies for assessing palatability and caution about using adult panels to predict palatability among children.

Alignment between stakeholders in defining acceptability, assessment methods and criteria would clearly foster much better understanding of the relationships between acceptability, swallowability and adherence to therapy. This relationship is essential to understand risks and develop appropriate mitigation strategies to achieving the desired therapeutic outcome.

4. SOLUTIONS

This section outlines some potential solutions for addressing the challenges described.

4.1 Seek advice from regulators as early as possible in the process of developing formulations

Building the much-needed consensus between regulators and the pharmaceutical industry around what is meant by age-appropriate medicines for children, what acceptability is and how acceptability should be assessed and reported will likely take considerable time. Nevertheless, before and during a marketing authorization procedure for a medicinal product, pharmaceutical companies have various opportunities to discuss critical issues in the drug development process with regulators.

Part of this dialogue is scientific advice, an opportunity for (early) communication between a company and a regulatory authority (the EMA and/or national competent authorities) on quality and both clinical and nonclinical aspects of drug development, such as study design, choice of endpoint and indication (see [http://www.ema.europa.eu/ema:Scientific advice and protocol assistance](http://www.ema.europa.eu/ema:Scientific_advice_and_protocol_assistance)).

The EMA scientific advice is open to pharmaceutical companies, academia and other parties developing medicines and is free of charge for questions related to children. The number of companies requesting scientific advice related to medicines for children has increased every year. In 2007, only 7.6% of scientific advice was related to children versus 24.4% in 2016. Companies conducting clinical development in accordance with scientific advice recommendations are more likely to be granted marketing authorization (58).

Opportunities for scientific advice from the FDA are similar. Most importantly, a parallel mechanism has been put in place for EMA and FDA reviewers to concurrently exchange with pharmaceutical companies their views on scientific issues during the development phase of new medicinal products. This increases the dialogue between agencies and pharmaceutical companies from the beginning of the life cycle of a new product, provides a deeper understanding of the basis of regulatory decisions, optimizes product development and avoids unnecessary testing replication or unnecessary diverse testing methods. Parallel EMA and FDA advice can be obtained at the request of the developer.

4.2 Clearly define the characteristics of users and products

As explained above, the final formulation is necessarily a compromise between the constraints of the molecules and the specific needs of children. Although at the planning stage of developing formulations for children, when early clinical studies involving adults have just been completed, little is known of what these constraints are. Carefully considering the characteristics of the target populations of children and caregivers in their environment as well as those of the medicinal product is very important when establishing the target product profile (59).

The following characteristics of the user should be considered:

- age: relative arbitrary characteristic of the classically defined age groups given the variability and non-linearity of body composition and physiological maturation;
- inherent ability: neurocognitive development and dependence on the caregiver;

- previous experience of the child with the formulation, ability to learn how to take a given product (60) specifically, immunologic functioning (CD4+ T-cell%and/or the ability of the caregiver to prepare the product or use a device (short- versus long-term acceptability);
- disease type and state: acute versus chronic, disease type and state that may affect the ability to take the product; need for multiple active pharmaceutical ingredients or co-treatments, such as for HIV, tuberculosis (TB) or malaria therapy and previous knowledge of the dosage form; and
- the sociocultural context of medicine use (40,61).

The following characteristics of a medicinal product should be considered:

- palatability: the most frequently measured attribute of acceptability;
- appearance: for example, colour, shape, embossing etc.;
- swallowability: size, shape and integrity of the dosage form, such as film coating;
- the complexity of modification before administration if required: determining the dose, weight band width and frequency of dose adjustment; over time, shift of responsibility from caregiver to children;
- fixed-dose combinations;
- the required dose: for example, the dosing volume, number of tablets, break marks etc.;
- the need for a vehicle: soft food or liquid, culturally and financially determined;
- the required dosing frequency and duration of treatment;
- the selected administration device (62), if any;
- the primary and secondary container closure system; weight and bulkiness; need for refrigeration and physical, chemical and microbial stability; specific storage requirements;

- the actual mode of administration that reflects understanding user instructions and the feasibility of following them and the device–user interface, such as dial, touch screen, indicators, operating instructions, packaging etc.; and
- associated adverse reactions, tolerability and risk of misdosing.

4.3 Consider all acceptability attributes simultaneously and study them systematically

All the elements of acceptability should be systematically explored among children of the relevant age groups and appropriately reported. This applies to questions of taste, smell and texture but also the swallowability of less traditional solid forms, such as pellets of different sizes with or without coating, granules and mini-tablets (dispersible or not).

In terms of palatability, it is important to determine to what extent the results obtained in the laboratory (such as electronic taste sensing systems and cell models), in animal models and through adult taste panels or evaluations by healthy adult volunteers can be extrapolated to children (17).

It is also necessary to determine whether the results of acceptability studies among children can be extrapolated to children in different age groups, or for different types of diseases, considering the volume of liquid to be administered or the size of multi-particulate granules, for example (42). The research carried out in recent years around the acceptability of mini-tablets or pellets is an example of this approach (63–70).

Box 5.1 lists acceptability domains, providers of information and data capture tools, with selected articles and reports to which the reader can refer.

Box 5.1. Acceptability domains, providers of information and data capture tools

What aspects and dimensions of acceptability are measured?

- Taste, swallowability, other (34,71–74)
- Ease of use, need for device or for vehicle (62,75–79)
- Accuracy of the dose administered and completeness of dose intake (5,80)

Who is providing the information on acceptability?

- Health-care professionals (80,81)
- Educated panels of adult testers or evaluators (82)
- Caregivers: observational versus proxy measures (27,61,83,84)
- Children: issue of outcomes reported by children (85)

What tools are used to capture and report acceptability?

- Hedonic scales, Likert scales or visual-analogue scales: the complexity must be age appropriate (41,53,86–89)
- Direct observation or recorded reaction: closing mouth, pushing the product or vehicle away, crying or spitting out; refusal to take the medicine; inability to swallow (41,85)
- Time taken by the nurse or caregiver to administer the medicine
- Other tools, such as electronic tongue, animal models, etc.

Adherence and effectiveness as indicators of acceptability (60,81,89,90)

4.4 Plan acceptability studies as early as possible

At the earliest conception of the strategy for developing formulations for children, all the dimensions of acceptability listed above must be considered. The need for data to inform the biopharmaceutical risk assessment should be identified early so its collection can be synchronized with the programme for developing formulations for adults. For example, these may include evaluating potential taste issues using animal models and trained adult taste panels.

When the adult dosage is being developed, an exploratory formulation is usually used for the Phase I and IIa studies. Based on these, a commercial formulation for adults may be developed. The development of a formulation for children starts much later (Fig. 5.2). When the paediatric investigation plan is submitted to regulators, the formulation for children can only be broadly described based on the exploratory formulation for adults used at the time.

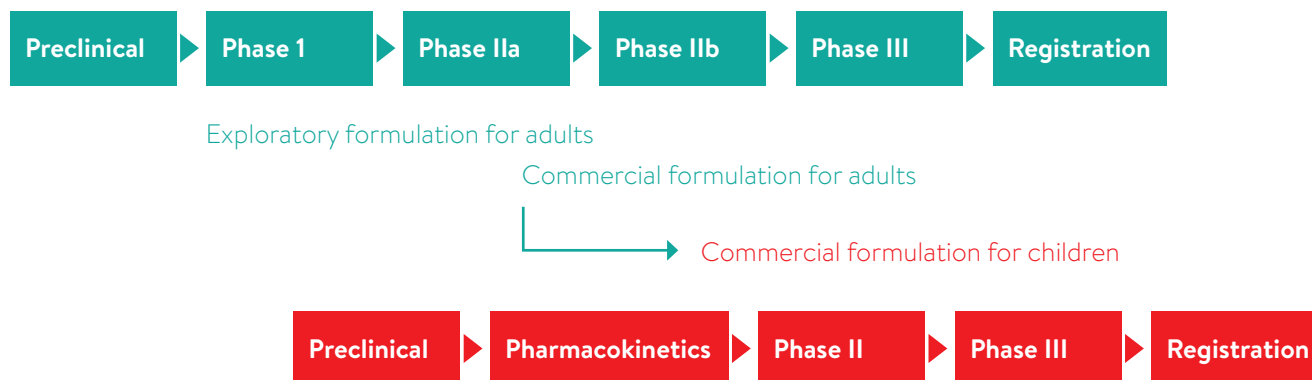
Acceptability for children can first be assessed during the initial dose-finding or population pharmacokinetic studies. All components of acceptability in the target populations must be evaluated to minimize the risk of delays in developing the final commercial formulation for children.

Acceptability in the target populations can thus be directly assessed and documented early when the formulation is being developed at the time of the initial dose-finding pharmacokinetic studies involving children. Using prototype formulations may limit the delays incurred if the formulation design needs to be modified based on the evaluation of acceptability.

Acceptability can still be further assessed in pre-registration or in post-marketing studies, but this would likely be too late to effectively inform the development of formulations for children. The data generated may only lead to modifying the product labelling or to amending the dosing instructions.

Fig. 5.2. Evaluating all aspects of acceptability in the first pharmacokinetic studies involving children

Developing formulations for adults



Developing formulations for children

4.5 Capitalize on existing scientific networks

If several hundred paediatric investigation plans or paediatric study plans have been submitted, it is only now that they start to result in registered products. It is therefore too early to draw the lessons learned from the first decade of implementation of the regulation of the development of formulations for children. Issues of stability, bioavailability and dose determination and the safety of excipients have largely dominated the scene and taken precedence over the question of acceptability. Nevertheless, the regulation of the development of formulations for children has set in motion considerable interest and debate around acceptability, as shown by the work of scientific networks regrouping academics and formulation scientists such as the European Paediatric Formulations Initiative and the IQ Consortium Drug Product Pediatric Working Group. All stakeholders agree on the need to systematically incorporate acceptability considerations within drug development without delaying the availability of therapies for children.

4.6 Harvest what is already available

Regulators, in collaboration with both the innovator and generic pharmaceutical companies, should work to identify opportunities to share key lessons learned and best practices based on their interactions. The types of information most valuable to developers should be reviewed and discussed, with agreement on the types of information that could be shared without disclosing the confidential proprietary data. Routinely making this information available to companies throughout the course of developing a paediatric investigation plan or paediatric study plan would facilitate the efficient development of a formulation for children.

The publication of best practices for evaluating acceptability by regulators would be helpful in planning and implementing the development of tailored formulations. The publication of best practices has been applied for Phase I studies, population pharmacology, efficacy and safety, extrapolation of data collected for adults and post-registration studies. Similar to the above, if alignment can be reached on what constitutes precompetitive sharing of best practices, this would greatly facilitate formulation assessments.

Although regulators should require that the essential elements that constitute the acceptability of a product in the various target groups be evaluated clinically in children, the pharmaceutical industry should re-evaluate their publication strategies with respect to the clinical results related to assessing the acceptability of drug products and devices in these trials. A strategy that mirrors the publication of clinical safety and efficacy endpoints could serve this purpose (25). This will progress biopharmaceutical science and minimize registration delays.

Regulatory agencies provide the opportunity for free scientific advice; pharmaceutical companies are therefore strongly advised to consult with regulators periodically or as needed to ensure strategic and technical alignment. This is especially true for the generic pharmaceutical industry, since it is playing an increasingly important role in providing medicines for children. The creation of fixed-dose combinations of several molecules poses problems that transcend the already complex issues of stability, compatibility and bioequivalence. Scientific advice and early interactions with regulators can help to minimize biopharmaceutical risks and speed up product registration.

4.7 Start to collect data systematically

Without unnecessarily increasing the complexity and duration of developing formulations for children, all the components of acceptability should be evaluated among the relevant users for all paediatric subsets of interest. This requires that the team in charge of interacting with the regulators, the scientists responsible for developing formulations and the clinical teams within a company work in close collaboration from the onset of the programme for developing formulations for children.

Paediatricians and paediatric research networks should systematically include in research protocols a module for assessing the acceptability of formulations for children in any clinical trial

involving children, in pharmacological studies to determine the dose that ensures optimal exposure across all age and weight bands and in the subsequent efficacy and safety studies. These evaluations are essential to better understand the longer-term acceptability of the drugs developed as well as the impact of acceptability on adherence and the outcomes of major interest: effectiveness and safety (15,91).

Children and their caregivers must be involved as early as possible in developing the medicines that are safe and designed for them. The participation of children and caregivers in clinical trials can contribute in a meaningful way. In many instances, the lack of children to participate in trials can slow recruitment and hinder the completion of clinical studies. This reality is a meaningful obstacle to developing products for children. This same reality makes it even more important that drug product and formulation elements are considered from the earliest stages of developing formulations for children to avoid changes late in development that further slow the registration of medicines for children.

4.8 Broaden acceptability studies to include cultural elements and involve social scientists

Not only children and their parents, but families and the broader community, health professionals, public health stakeholders and civil society organizations should be more involved in studying the acceptability of formulations (see the module on community engagement). Geographical and cultural environment should be considered, especially in countries in which patients have limited access to health care (15,40). Parents are often not frontline caregivers, either because they have health problems themselves or because they are absent. The extended family of brothers and sisters or grandparents are in turn responsible for ensuring that children receive the medications they need. The conditions for delivering and storing drugs and the availability of foods and vehicle types

vary considerably from place to place. The design of formulations, packaging and instructions to users must take these circumstances into account (57,92).

Social scientists must be involved in this research to better understand the use of drugs in the economic, geographical and cultural context of their use. This goes beyond the supposed but very poorly documented variation in taste preferences across cultures. For example, the ability of parents or caregivers and children to use a drug depends in part on the community's perception of the disease in question and the expected role of the therapy and of the health-care system that makes it available (90). The stigmatization of HIV infection has raised public awareness of these issues, but the same considerations apply to managing other diseases, whether TB, malaria or chronic diseases among children.

4.9 Encourage methodological and translational research

Academia and formulation scientists must undertake more primary fundamental and translational research, with the support of government organizations such as the United States National Institutes of Health or philanthropic organizations such as the Bill & Melinda Gates Foundation, in addition to or even in collaboration with the work being done in the pharmaceutical industry.

Methodological research is needed. It should cover the study designs (validated scales for endpoint assessment, children versus adults as assessors, power analyses and sample sizes, use of controls and need for randomization and single-dose versus

multi-dose studies) and their standardization, the evaluation of the reliability and reproducibility of the results and the analysis of the data. The tools for collecting acceptability data need to be validated according to age groups, the greater or lesser involvement of parents or guardians and the economic and cultural context in which children live. The methods, strengths and limitations of patient-reported outcome studies that collect data to support claims in medical product labels need to be assessed. Standardized methods would enable comparisons across studies and define which products are better accepted in which populations.

Standardized, universal, objective, simple metrics must be developed and validated to evaluate the acceptability of existing formulations for children and optimize that of formulations under development. This research must necessarily involve the concerned populations, researchers and regulators. Multicomponent referential models to assess acceptability are currently being evaluated (mapping and clustering models) (80).

This research must also be translated to enrich decision-making models that would allow, at the planning stage of the development of formulations for children, the best options for dose forms for children to be determined with the best degree of reliability. These models should accelerate the development of appropriate formulations for children with the effect of increasing efficiency for all stakeholders and delivering optimized medical outcomes to children.

5. CASE STUDIES

This section describes two examples of situations where acceptability was considered in developing pharmaceutical products.

5.1 Developing ritonavir and lopinavir/ritonavir for treating children with HIV

Ritonavir and lopinavir (LPV) are very potent ARV drugs that have been widely used in combination with various nucleoside reverse-transcriptase inhibitors for treating people living with HIV since the early 2000s. One important characteristic is that they present a solid barrier to the emergence to resistance mutations. They have therefore been extensively used as a second-line regimen for adults and as first- and second-line regimens for children whose initial viral load is very high compared with that of adults. However, both drugs are insoluble and poorly absorbed. The initial formulations developed by the innovator pharmaceutical company AbbVie were complex solutions presented in soft-gel capsules for both adults and children or as liquid formulations for children with excipients, which made their taste difficult to bear. In the late 2000s, AbbVie subsequently developed a solid formulation using the melt-extrusion technology that resolved taste and excipient issues, presented in the form of tablets for adults and smaller tablets for older children.

The generic company Cipla has more recently developed a pellet formulation of the LPV/ritonavir (LPV/r) combination for infants and young children in resource-limited settings (with tentative approval by the FDA), but as shown in the study summarized below, taste remains a significant challenge for younger children, and swallowability creates difficulty in using this formulation for infants younger than three months of age. Cipla in collaboration with the Drugs for Neglected Diseases initiative is further

developing a taste-masked formulation with solid granules that associates four drugs LPV, ritonavir, abacavir and lamivudine, a 4-in-1 with the aim of resolving the limitations of the pellets and simplifying therapy for infants (93).

Finally, AbbVie has successfully developed and commercialized a solid powder formulation of ritonavir to replace the liquid formulation, which needs refrigeration for storage and is therefore difficult to use in the tropical climates of Africa, where more than 95% of children living with HIV reside. Ritonavir is used as a booster for other protease inhibitors.

The publication of this development by AbbVie is forthcoming. Indeed, the case of LPV and ritonavir exemplifies the complexities of developing age-appropriate medicines for children when the chemistry of the active ingredients severely limits formulation options.

5.2 Example of acceptability evaluation embedded in a Phase II comparative bioavailability study of a generic versus an innovator product

WHO and national guidelines recommend LPV/r for children younger than three years initiating first-line antiretroviral therapy (ART) and older ones requiring second-line ART. Whereas older children (older than five years) who can swallow tablets may have minimal problems taking their medications, the younger ones would need a syrup, pellet or mini-tablet or dispersible formulation. Although currently licensed formulations of LPV/r syrup and pellets taste bitter, in the CHAPAS-2 trial in Uganda comparing solid and liquid formulations, the pellets were more acceptable than syrup largely because they were easier to store and transport, since they are heat stable and hence

do not require refrigeration. However, the acceptability of the pellets waned over time, with the reported challenges being the need to mask the bitter taste with food, increasingly refused by the children, and the caregivers worrying about ensuring that the child is taking the whole dose. The requirement that the LPV/r syrup be refrigerated makes the formulation less acceptable than heat-stable pellets in low- and middle-income countries, although the pellet

formulation remains less than ideal because it tastes bitter. In CHAPAS-2, the older children preferred LPV/r tablets to pellets, and taste was the main factor. An LPV/r formulation suitable for younger children with improved taste masking therefore still needs to be developed. In the meantime, ongoing caregiver support needs to be embedded in national programmes in the countries in which the LPV/r pellets have been rolled out (94–96).

6. SUMMARY

The acceptability of a drug formulation to the intended users may have a significant impact on treatment adherence and ultimately safety and efficacy. As a result of recent paediatric regulations in the United States and the European Union, considerable effort has been made to improve the acceptability of drug formulations for children. However, acceptability studies are often carried out late

in the drug development timeline, and there is little consensus about how acceptability should be defined, measured and reported. This may contribute to unnecessary delays in making new medicines available to children. The considerations below aim to promote clearer and more systematic evaluation of the acceptability of new formulations for children to facilitate their development.

7. KEY CONSIDERATIONS

- Consensus around assessing the acceptability of formulations for children should be established among key experts.
- Standard criteria for measuring acceptability should be developed.
- Risk-based strategic approaches should be used to guide the selection of formulations.
- The characteristics of users and products should be clearly defined and considered simultaneously.
- Acceptability studies should be planned early in the process of drug development.
- Regulators should make available existing non-proprietary data on acceptability.
- Acceptability data should be collected systematically.
- Acceptability studies should be broadened to include cultural elements, and social scientists should be involved.
- Methodological and translational research relating to the acceptability of formulations should be encouraged.

8. USEFUL RESOURCES

- European Paediatric Formulations Initiative: www.eupfi.org
- IQ Consortium Drug Product Pediatric Working Group: www.iqconsortium.org
- United States Pediatric Formulations Initiative: www.bpca.nichd.nih.gov/prioritization/researchandcollaborations/Pages/pediatric-formulations-initiative
- Global Research in Paediatrics (GRIP) work package 5: Paediatric Formulations: www.grip-network.org
- Pediatric Formulations Task Force (American Association of Pharmaceutical Scientists)

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